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Short Report: Treatment

Effects of rosuvastatin and atorvastatin on glycaemic control in Type 2 diabetes—the CORALL study

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Abstract

Aims To examine whether high-dose statin therapy in Dutch European patients with Type 2 diabetes and dyslipidaemia influenced variables of glycaemic control.

Methods The CORALL study, which was a 24-week, open-label, randomized, parallel-group, phase IIIb, multi-centre study, was designed to compare the cholesterol-lowering effects of rosuvastatin compared with atorvastatin in patients with Type 2 diabetes. Fasting plasma glucose levels and HbA_{1c} levels were collected at baseline and at 6 and 18 weeks.

Results Treatment with the highest dose of statins, i.e. atorvastatin 80 mg and rosuvastatin 40 mg at 18 weeks from baseline, was associated with increase in HbA_{1c} levels; baseline 57 ± 11 mmol/l (7.4 ± 1.0%) to 61 ± 14 mmol/mol (7.7 ± 1.3%) (range 5.0–11.9) for atorvastatin ($P = 0.003$) and from baseline 60 ± 11 mmol/mol (7.6 ± 1.0%) to 63 ± 13 mmol/mol (7.9 ± 1.2%) (range 5.7–12.3) for rosuvastatin ($P < 0.001$). Mean fasting plasma glucose increased from baseline 8.7 ± 2.4 mmol/l to 9.5 ± 3.0 mmol/l upon treatment with atorvastatin 20 mg ($P = 0.002$) and 9.0 ± 3.0 mmol/l after treatment with 80 mg (not significant compared with baseline). The mean fasting plasma glucose did not change after treatment with rosuvastatin (9.1 ± 2.7 mmol/l at baseline, 8.9 ± 2.7 mmol/l with 10 mg, 9.4 ± 2.9 mmol/l with 40 mg).

Conclusions Glycaemic control deteriorated in patients with diabetes following high-dose statin therapy. Future controlled studies are needed to verify these findings and, if confirmed, determine whether such changes represent a true decline in glycaemic control. Presently, it appears that, based on the overwhelming prospective trial data available, the preventive effect of statin therapy supersedes that of the slight increase in HbA_{1c}.

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Keywords advanced glycation end products, diabetes mellitus, HbA_{1c}, statins

Introduction

3-Hydroxyl-3-methylglutaryl-coenzyme A (HMG-CoA) reductase inhibitors (statins) protect against cardiovascular disorders such as coronary heart disease and ischaemic cerebrovascular disease. Several large-scale studies have reported that high-risk patients, for example those with existing cardiovascular disease and Type 2 diabetes mellitus, show a considerable clinical benefit from statin treatment, and clinical guidelines recommend prescription of statins in such patients irrespective of baseline serum cholesterol levels [1–4]. Statins have an acceptable safety and tolerability profile [5].

However, recently a well-conducted meta-analysis of randomized trials reported a 9% higher risk of development of diabetes in statin users compared with placebo (odds ratio 1.09; 95% CI 1.02–1.17) [6]. Furthermore, in a recently published pooled analysis of data from five statin trials, high-dose statin therapy was associated with a 12% more risk of new-onset diabetes compared with moderate-dose statin therapy [7]. High-dose atorvastatin treatment compared with placebo in the Stroke Prevention by Aggressive Reduction in Cholesterol Levels (SPARCL) trial was even associated with a 44% increased risk of new-onset diabetes [8].

Deterioration of glycaemic control has been observed after initiation of atorvastatin therapy in patients with Type 2

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diabetes mellitus in Japan [9,10]. In a retrospective study, Takano *et al.* compared the effect of atorvastatin and pravastatin on glycaemic control in people with diabetes [9]. HbA_{1c} increased from 51 ± 10 mmol/mol (6.8 ± 0.9%) to 55 ± 12 mmol/mol (7.2 ± 1.1%) ($P < 0.001$) only in the atorvastatin group after 3 months of treatment. Somewhat similar findings have been observed in a prospective study in people with diabetes as well as those without diabetes [12,13]. One of the mechanisms for the detrimental effects of statins on glucose metabolism, at least of atorvastatin, could be the decreased expression of insulin-sensitive solute carrier family 2 (facilitated glucose transporter), member 4 (SLC2A4, formerly known as GLUT4) [10].

As part of the CORALL study [14], we examined whether 18 weeks of high-dose statin therapy in Dutch European patients with Type 2 diabetes and dyslipidaemia influenced variables of glycaemic control.

Research design and methods

The CORALL study was a 24-week, open-label, randomized, parallel-group, phase IIIb, multi-centre study. The first 6 weeks of the study was a dietary lead-in period, after the patients who fulfilled all inclusion criteria and none of the exclusion criteria were randomized to receive either rosuvastatin or atorvastatin. The study was designed to compare the cholesterol-lowering effects of rosuvastatin with atorvastatin in patients with Type 2 diabetes. Subjects were evaluated for efficacy on an intention-to-treat analysis, which contained all randomized subjects with known baseline data. A detailed description of the CORALL study has been previously reported [14]. Four hundred and sixteen subjects with dyslipidaemia and Type 2 diabetes mellitus were enrolled in the study; of those, 263 patients fulfilled the entry criteria and were randomized to either rosuvastatin (n = 131) or atorvastatin (n = 132). The patients were treated with either rosuvastatin 10 mg or atorvastatin 20 mg for 6 weeks, followed by force titration to rosuvastatin 20 mg (if initially on rosuvastatin 10 mg) or atorvastatin 40 mg (if initially on atorvastatin 20 mg) for 6 weeks and, finally, for another 6 weeks, the patients were treated with rosuvastatin 40 mg (if initially on rosuvastatin 20 mg) or atorvastatin 80 mg (if initially on atorvastatin 40 mg). Fasting plasma glucose and HbA_{1c} levels were collected at baseline and at 6 and 18 weeks. HbA_{1c} was measured in a central laboratory by high-performance liquid chromatography (Bio-Rad Variant II Automated Glycosylated Hemoglobin Analyzer; Bio-Rad Laboratories, Hemel Hempstead, UK) with a normal range 26–44 mmol/mol (4.5–6.2%). Plasma glucose levels were analysed by the hospitals' central laboratories, with normal reference range as measured by high-performance liquid chromatography, and plasma glucose measured by the hexokinase method.

Statistical analysis

SPSS version 16.0 (SPSS Inc., Chicago, IL, USA) was used for statistical analysis. Data are given as mean ± SD. The statistical analysis of the data was carried out with the paired results obtained at baseline and at 6 weeks and 18 weeks after initiation of rosuvastatin or atorvastatin medication using the Wilcoxon matched-pairs signed-ranks test and repeated measures analysis of variance (ANOVA). P-values below 0.05 were considered statistically significant.

Results

Table 1 depicts the baseline characteristics, with typical age, BMI and blood pressure distribution for this population. No significant change in body weight was observed during the study (data not shown). The percentage of patients reaching target LDL cholesterol values of < 2.5 mmol/L (European Atherosclerosis Society guideline) was 77.7, 83.1 and 90.0% with rosuvastatin after 6 weeks (10 mg), 12 weeks (20 mg) and 18 weeks (40 mg), respectively, whereas this goal was reached by 70.5,

Table 1 Baseline characteristics of patients

Demographic characteristics	Rosuvastatin n = 131	Atorvastatin n = 132	Total n = 263
Gender (men/women)	59/72	63/69	122/141
Age (years)	61 ± 9	59 ± 10	60 ± 10
BMI (kg/m^2)	31.8 ± 6.1	31.0 ± 6.0	31.4 ± 6.1
Systolic blood pressure (mmHg)	145 ± 20	148 ± 17	147 ± 19
Diastolic blood pressure (mmHg	82 ± 8	83 ± 8	83 ± 8
HbA_{1c} (mmol/mol) (%)	60 ± 11 7.6 ± 1.0	57 ± 11 7.4 ± 1.0	58 ± 11 7.5 ± 1.0
Mean fasting plasma glucose (mmol/l)	9.1 ± 2.7	8.7 ± 2.4	8.9 ± 2.6
Diet only	3 (2)	2 (2)	5 (2)
Oral blood glucose-lowering agents	40 (31)	47 (35)	87 (33)
Insulin	88 (67)	83 (63)	171 (65)
Hypertension	79 (60)	86 (65)	165 (63)

Baseline data are mean ± sd or absolute number (%). There were no significant differences between both treatment groups.

76.5 and 78.0% with atorvastatin after 6 weeks (20 mg), 12 weeks (40 mg) and 16 weeks (80 mg), respectively.

Six weeks' treatment with atorvastatin 20 mg or rosuvastatin 10 mg did not change the HbA_{1c} levels significantly [HbA_{1c} levels of 58 ± 12 mmol/mol (7.5 ± 1.1%) in both treatment groups) as compared with baseline [HbA_{1c} 60 ± 11 mmol/mol (7.6 ± 1.0%) for rosuvastatin and 57 ± 11 mmol/mol (7.4 ± 1.0%) for atorvastatin, respectively] (Fig. 1). However, treatment with the highest dose of statins, i.e. atorvastatin 80 mg and rosuvastatin 40 mg at 18 weeks from baseline was associated with statistically significant increase in HbA_{1c} levels: 61 ± 14 mmol/mol (7.7 ± 1.3%) [range 31–107 mmol/mol (5.0–11.9%)] for atorvastatin ($P = 0.003$) and 63 ± 13 mmol/mol (7.9 ± 1.2%) [range 39–111 mmol/mol (5.7–12.3%)] for rosuvastatin ($P < 0.001$), respectively, as compared with baseline (Fig. 1). The change in LDL cholesterol and HbA_{1c} were not related.

Mean fasting plasma glucose increased from baseline 8.7 ± 2.4 to 9.5 ± 3.0 mmol/l upon treatment with atorvastatin 20 mg ($P = 0.002$) and 9.0 ± 3.0 mmol/l after treatment with 80 mg atorvastatin (not significant compared with baseline). The mean fasting plasma glucose did not change significantly after treatment with rosuvastatin (9.1 ± 2.7 mmol/l at baseline, 8.9 ± 2.7 mmol/l with rosuvastatin 10 mg, 9.4 ± 2.9 mmol/l with rosuvastatin 40 mg).

Discussion

Among Dutch Caucasian patients with dyslipidaemia and Type 2 diabetes, we found that (high-dose) statin therapy leads to a small but significant increase of HbA_{1c} levels.

Caucasian patients with Type 2 diabetes mellitus have been included in many statin studies, but the effect of statin therapy on glycaemic control has only been scarcely reported. In the Collaborative Atorvastatin Diabetes Study (CARDS) the patients with Type 2 diabetes treated with atorvastatin 10 mg over 4 years had a mean HbA_{1c} of 67 mmol/mol (8.3%) [at baseline 63 ± 15 mmol/mol (7.87 ± 1.42%)] and the patients on placebo had a mean of 65 mmol/mol (8.1%) [at baseline 62 ± 15 mmol/mol (7.81 ± 1.39%)] [1]. These results should be interpreted with care, because the glycaemic control variables refers to only those patients who reached the 4-year point. This might either under- or overstate any effect of atorvastatin on glycaemic control. Although the initial dose of atorvastatin therapy was higher in our study (20 mg), no change in HbA_{1c} levels as compared with baseline was observed. It may be that the relatively short time course (6 weeks) of initial atorvastatin therapy was the reason for the difference with CARDS, although it cannot be excluded that there are dose–response effects. A randomized, double-blind, double-dummy, multicentre, phase IIIb, parallel-group study to compare the efficacy and safety of rosuvastatin (10 mg and 20 mg) and atorvastatin (10 mg and 20 mg) in patients with Type 2 diabetes mellitus (ANDROMEDA) study, the mean HbA_{1c} increased from 52 mmol/mol (6.9%) at baseline to 56 mmol/mol (7.3%) at week 16 with rosuvastatin 20 mg/day, and from 53 mmol/mol (7.0%) at baseline to 56 mmol/mol (7.3%) at week 16 with atorvastatin 20 mg/day [13]. The difference with our study is that, in ANDROMEDA, the statin therapy was given at a fixed dose during a fixed time course.

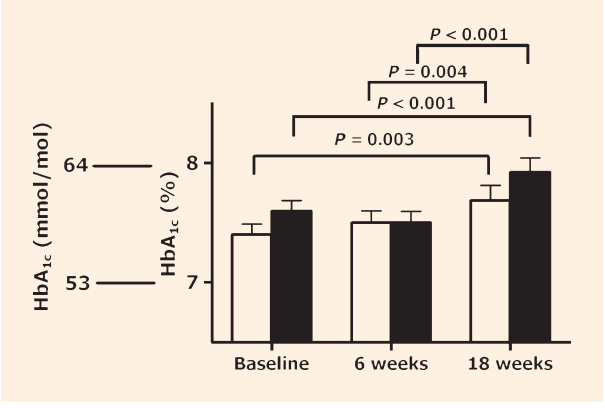

FIGURE 1 Time course changes in HbA_{1c} levels in patients with Type 2 diabetes administered with atorvastatin (□) or rosuvastatin (■); 6 weeks atorvastatin 20 mg and rosuvastatin 10 mg; 18 weeks atorvastatin 80 mg and rosuvastatin 40 mg.

In the Atorvastatin in Factorial with Omega-3 EE90 Risk Reduction in Diabetes (AFORRD) study, an increase in HbA_{1c} of 1.5 mmol/mol (0.3%) ($P < 0.0001$) after atorvastatin (20 mg/day) intervention, but no significant change in the Omega-3 EE90 (2 g/day) intervention after 4 months [14].

There are a few limitations to this study that need to be addressed. The most important limitations are that we did not have a placebo-control arm and the relatively short duration of this study. Furthermore, this study was not powered to find a difference in the glycaemic control. In addition, it may be questioned whether the HbA_{1c} increase is a real consequence of worsening of glycaemic control, as neither CARDS nor ANDROMEDA reported an increase in dose of blood glucose-lowering agents, which may be the case when doctors or participating patients witness an increase in blood glucose levels.

In conclusion, this short-term study of intensive statin therapy in patients with diabetes suggests a small but significant increase of HbA_{1c} in statin recipients. Future controlled studies are needed to verify these findings and, if confirmed, determine whether such changes represent a true decline in glycaemic control, or some other mechanism perhaps linked to reduced oxidative potential. Furthermore, whether this change remains in the longer term, and has long-term implications, needs to be studied before making any judgment on clinical relevance of these observations. Presently, it appears that, based on the overwhelming prospective trial data available, the preventive effect of statin therapy supersedes that of the slight increase in HbA_{1c}.

Competing interests

BHRW was principal investigator of the CORALL study, which has been financially supported by Astra Zeneca. The

authors of this paper independently analysed the data and wrote the entire manuscript. The sponsor has reviewed the study manuscript, but the review had no influence on the contents of the manuscript or its conclusions. The principal investigator fully controlled the decision to submit for publication.

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